Impact of luspatercept versus epoetin alfa treatment on genomic landscape and mutational burden in patients with lower-risk myelodysplastic syndromes in the COMMANDS trial

PS1610

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Introduction

- Myelodysplastic syndromes (MDS) are myeloid neoplasms characterized by ineffective hematopoiesis, which leads to cytopenias (commonly anemia), dysplastic bone marrow changes, and clonal expansion[1]
- Progressive anemia is the most common complication of lower-risk MDS (LR-MDS) and eventually requires a red blood cell (RBC) transfusion[2]
  - Approximately 30% of patients with LR-MDS will experience disease progression to acute myeloid leukemia[3]
- Erythropoiesis-stimulating agents (ESAs), such as epoetin alfa, benefit ~35% of patients with LR-MDS by treating anemia and reducing transfusion needs, but resistance within 2 years is common
  - Baseline erythropoietin ≤ 200 U/L and ≤ 2 somatic mutations predict better response, while driver gene mutations are linked to worse outcomes[4-6]
- Luspatercept demonstrated superior clinical benefit over epoetin alfa (60.4% vs 34.8% reached the primary endpoint; $P < 0.0001$) for the treatment of anemia in transfusion-dependent patients with LR-MDS in the phase 3 COMMANDS trial (NCT03682536)[7]
  - RBC transfusion dependency (TD) is a prognostic factor in MDS, and treatments that reduce RBC TD could impact overall survival (OS)
  - Responder analyses revealed that luspatercept reduced anemia and transfusion burden (TB) versus epoetin alfa, irrespective of genomic landscape/burden, variant allele frequency (VAF), and ring sideroblast (RS) status[8]
- The International Prognostic Scoring System (IPSS)-Revised (R) and the newer IPSS-Molecular (M) stratify patients for progression risk using hematologic parameters, bone marrow blasts, cytogenetics, and gene mutations
- However, the impact of luspatercept and ESAs on the longitudinal mutational landscape and IPSS-M risk stratification remains unknown

Objective

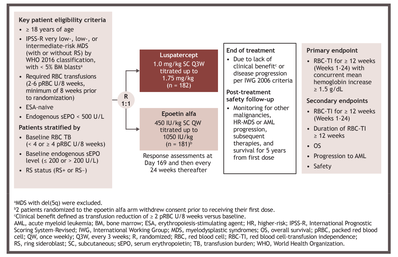
- To characterize gene mutational prevalence at baseline, IPSS-M risk, and longitudinal clonal changes after luspatercept versus ESA and their association with clinical outcomes

Methods

Study design

- COMMANDS is a phase 3, open-label, randomized trial comparing luspatercept versus epoetin alfa to treat anemia due to LR-MDS in patients who require RBC transfusions (**Figure 1**)
- The primary endpoint of COMMANDS was achievement of RBC-transfusion independence (RBC-TI) for ≥ 12 weeks with a concurrent mean hemoglobin (Hb) increase ≥ 1.5 g/dL during Weeks 1 to 24

Figure 1. COMMANDS study design



[a]MDS with del(5q) were excluded.
[b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose.
[c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC U/8 weeks versus baseline.
AML, acute myeloid leukemia; BM, bone marrow; ESA, erythropoiesis-stimulating agent; HR, higher-risk; IPSS-R, International Prognostic Scoring System-Revised; IWG, International Working Group; MDS, myelodysplastic syndromes; OS, overall survival; pRBC, packed red blood cell; QW, once weekly; Q3W, every 3 weeks; R, randomized; RBC, red blood cell; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; SC, subcutaneous; sEPO, serum erythropoietin; TB, transfusion burden; WHO, World Health Organization.

- In patients who consented to biomarker analyses, bone marrow samples were collected at screening and during treatment throughout the COMMANDS study and were sequenced using targeted sequencing and whole-genome sequencing (WGS)
  - Targeted next-generation sequencing covered 82 myeloid-related genes at a median exon coverage of 2400 × and 3% sensitivity (NovaSeq 6000, Illumina®)
  - At screening, 350 of 361 patients were profiled; 212 and 160 patients were profiled at Weeks 24 and 48, respectively
  - WGS was conducted on 153 patients at baseline only at a median exon coverage of 80 ×
- IPSS-M category was determined for each patient using cytogenetics, mutations, and percent blasts[9]
- Survival outcomes were analyzed using the Kaplan-Meier method
  - Multivariable regression and Cox regression models examined the effects of treatment after adjusting for relevant variables, including change in Hb, RS status, mutational burden, baseline IPSS-M risk, and IPSS-M risk downstaging
  - Statistical analyses were conducted using R with significance set at $P < 0.05$
- Targeted next-generation sequencing gene panel (82 genes)
  - *APC*, *ASXL1*, *ASXL2*, *ATM*, *ATRX*, *BCOR*, *BCORL1*, *BRAF*, *BRCC3*, *CALR*, *CBL*, *CDH23*, *CDKN2A*, *CEBPA*, *CREBBP*, *CSF3R*, *CSNK1A1*, *CTCF*, *CUX1*, *DDX41*, *DDX54*, *DHX29*, *DNMT3A*, *EP300*, *EPOR*, *ETNK1*, *ETV6*, *EZH2*, *FANCL*, *FBXW7*, *FLT3*, *FLT3-ITD*, *GATA1*, *GATA2*, *GNAS*, *GNB1*, *IDH1*, *IDH2*, *IL6R*, *JAK2*, *KDM5A*, *KDM6A*, *KIT*, *KMT2D*, *KRAS*, *MPL*, *MYC*, *MYD88*, *NF1*, *NOTCH1*, *NPM1*, *NRAS*, *PDGFRA*, *PDGFRB*, *PHF6*, *PIGA*, *PPM1D*, *PRPF8*, *PTEN*, *PTPN11*, *RAD21*, *RB1*, *RUNX1*, *SETBP1*, *SF1*, *SF3A1*, *SF3B1*, *SH2B3*, *SMC1A*, *SMC3*, *SRSF2*, *STAG2*, *SUZ12*, *TET2*, *TP53*, *U2AF1*, *U2AF2*, *UBA1*, *WT1*, *ZBTB7A*, *ZEB2*, *ZRSR2*

Results

- Baseline patient characteristics and outcomes between the luspatercept and epoetin alfa arms in the biomarker cohort are presented in **Table 1**
- The 2 arms were generally balanced, with no significant differences observed ($P > 0.05$) for variables such as age, sex, race, RBC TB, baseline serum erythropoietin, IPSS-R/M risk, ECOG performance status score, platelets, Hb, RS status, *SF3B1* mutation status, and OS, with the exception of the primary endpoint and time from MDS diagnosis

Table 1. Baseline characteristics of the COMMANDS study biomarker cohort

	Epoetin alfa (n = 179)	Luspatercept (n = 182)	*P* value
Age, years *Mean* (SD)	73 (9.7)	73 (8.9)	1
Sex, n (%) Female Male	89 (49.7) 90 (50.3)	73 (40.1) 109 (59.9)	0.1
Race, n (%) Asian White Other	25 (14.0) 141 (78.8) 13 (7.3)	19 (10.4) 146 (80.2) 17 (9.3)	0.49
RBC TB (screening period), n (%) < 4 RBC U/8 weeks ≥ 4 RBC U/8 weeks	119 (66.5) 60 (33.5)	120 (65.9) 62 (34.1)	1
Baseline sEPO, n (%) ≥ 200 U/L > 200 U/L	140 (78.2) 39 (21.8)	142 (78.0) 40 (22.0)	1
IPSS-R at baseline, n (%) High Intermediate Low Very low Missing	0 29 (16.2) 131 (73.2) 17 (9.5) 2 (1.1)	1 (0.55) 34 (18.7) 130 (71.4) 16 (8.8) 1 (0.55)	0.71
IPSS-M at baseline, n (%) Very high High Moderate high Moderate low Low Very low Missing	4 (2.2) 17 (9.5) 28 (15.6) 34 (19.0) 87 (48.6) 3 (1.7) 6 (3.4)	2 (1.1) 22 (12.1) 25 (13.7) 49 (26.9) 79 (43.4) 2 (1.1) 3 (1.6)	0.5
Time since diagnosis, n (%) < 1 year > 1 to ≤ 2 years > 2 to ≤ 5 years > 5 years	121 (67.6) 21 (11.7) 22 (12.3) 15 (8.4)	103 (56.6) 26 (14.3) 31 (17.0) 22 (12.1)	0.19
Time from MDS diagnosis, years *Median* (IQR)	0.41 (1.34)	0.66 (2.2)	0.03
Baseline platelet count,[a] × 10⁹/L *Mean* (SD)	249 (135)	238 (124)	0.86
Baseline Hb, g/dL *Mean* (SD)	7.6 (0.93)	7.6 (0.87)	0.74
RS status, n (%) Negative Positive	52 (29.1) 127 (70.9)	50 (27.5) 132 (72.5)	0.83
Baseline *SF3B1* status, n (%) Mutated Non-mutated Missing	100 (55.9) 71 (39.7) 8 (4.5)	114 (62.6) 65 (35.7) 3 (1.6)	0.37
Patient somatic mutation status, n (%) No mutation ≥ 1 mutation Missing	15 (8.4) 156 (87.2) 8 (4.5)	15 (8.2) 164 (90.1) 3 (1.6)	1
Primary endpoint, n (%) Responders Non-responders	63 (35.2) 116 (64.8)	110 (60.4) 72 (39.6)	1.9e-06
OS, months[b] *Median* (CI)	46 (38.4-NA)	NA (47.3-NA)	0.12

[a]Baseline platelet count was missing for 1 patient in the luspatercept arm.
[b]NA indicates that median survival probability was not reached.
Hb, hemoglobin; IPSS-M/R, International Prognostic Scoring System-Molecular/Revised; MDS, myelodysplastic syndromes; NA, not applicable; OS, overall survival; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; TB, transfusion burden.

- At baseline, 320/350 (91%) patients had somatic mutations in ≥ 1 gene, with most VAFs ranging from 3% to 50% (median, 32%)
  - The most common mutations were balanced between the luspatercept and epoetin alfa arms: *SF3B1* (64% vs 60%), *TET2* (35% vs 34%), *ASXL1* (23% vs 20%), *DNMT3A* (17% in both), *U2AF1* (9% vs 13%), *SRSF2* (12% vs 8%), and *EZH2* (7% vs 6%; **Figure 2**)
- Gene prevalence in the luspatercept and epoetin alfa arms, which was measured at baseline, Week 24, and Week 48, is presented in **Figure 2**
  - The bar plot shows that 227 out of 275 (83%) baseline genetic variants remained consistent post-treatment
  - Notable genes (ie, *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1*) were the most prevalent across both arms
  - The spectrum of mutations remained generally stable at Weeks 24 and 48
- There were no significant changes over time in the number of variants in the overall population, by responder, RS status, or between arms, although few patients exhibited variant gain/loss at post-treatment versus baseline (**Figure 3**)
- Persistent, lost, and newly gained gene variants at Week 24 or 48 post-treatment were compared between the luspatercept and epoetin alfa arms (**Figure 4**)
  - Most gene variants were persistent post-treatment relative to baseline, and the median VAF of infrequent gained/lost variants at any time post-treatment was 3.06% (48/275), near the gene detection limit

Figure 2. Gene prevalence between the luspatercept and epoetin alfa arms at baseline, Week 24, and Week 48

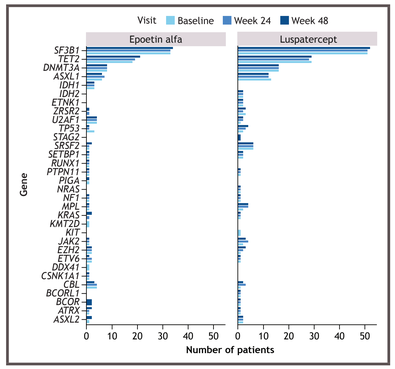
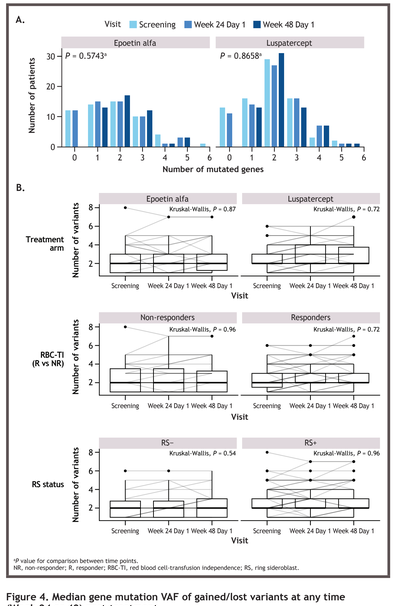
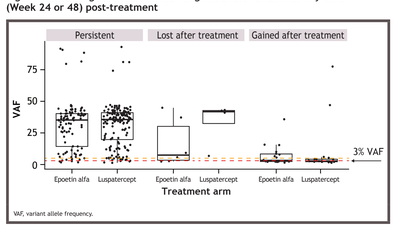


Figure 3. Longitudinal changes in the number of variants in the luspatercept and epoetin alfa arms, stratified by mutational burden, treatment arm, RBC-TI response, and RS status



[a]P value for comparison between time points.
NR, non-responder; R, responder; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast.

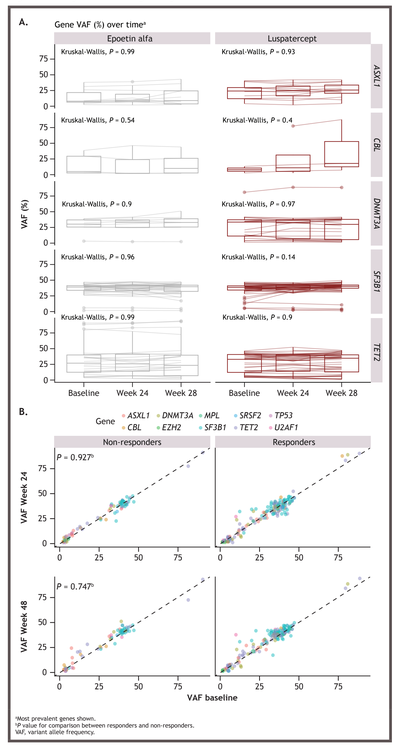
Figure 4. Median gene mutation VAF of gained/lost variants at any time (Week 24 or 48) post-treatment



VAF, variant allele frequency.

- Overall, the longitudinal VAF changes across genes were not statistically significant (Week 24/48 vs baseline; **Figure 5A**), nor were any associations found between patient-wise VAF changes and clinical response ($P > 0.05$; **Figure 5B**)

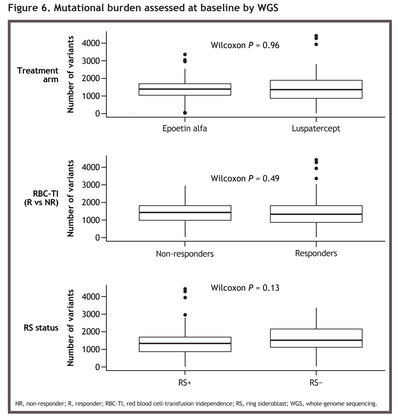
Figure 5. Longitudinal changes in gene mutation VAF



[a]Most prevalent genes shown.
[b]P value for comparison between responders and non-responders.
VAF, variant allele frequency.

- When the mutational assessment was expanded from targeted sequencing to WGS at baseline (**Figure 6**), there were no significant differences in mutational burden across subgroups, suggesting a uniform distribution of gene variants across treatment arms, clinical response groups, and RS status

Figure 6. Mutational burden assessed at baseline by WGS



NR, non-responder; R, responder; RBC-TI, red blood cell-transfusion independence; RS, ring sideroblast; WGS, whole-genome sequencing.

- Numerically more patients experienced an IPSS-M risk category downstaging with luspatercept (66/121, 54%) versus epoetin alfa (43/97, 44%; **Figure 7**); among these patients, Hb increases (≥ 1.5 g/dL) occurred in 85% (56/66) of patients in the luspatercept arm versus 81% (35/43) of patients in the epoetin alfa arm

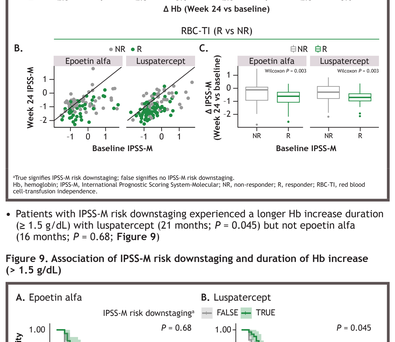
Figure 7. IPSS-M risk downstaging with luspatercept versus epoetin alfa

A.

IPSS-M risk downstaging at Week 24				
	Epoetin alfa		Luspatercept	
	IPSS-M risk downstaging[a]			
Baseline: IPSS-M[a]	FALSE	TRUE	FALSE	TRUE
Very low	3	0	2	0
Low	43	8	39	20
Moderate low	4	12	10	25
Moderate high	4	11	3	10
High	0	9	1	9
Very high	0	3	0	2

	Epoetin alfa	Luspatercept
Persistent IPSS-M IPSS-M risk downstaging	54	55
	43 (44%)	66 (54%)
	Fisher's exact test *P* value: 0.17	

B.



[a]True signifies IPSS-M risk downstaging; false signifies no IPSS-M risk downstaging.
IPSS-M, International Prognostic Scoring System-Molecular.

- In both treatment arms, IPSS-M risk downstaging was enriched in the responder group (ie, achievement of RBC-TI for ≥ 12 weeks with a concurrent mean Hb increase ≥ 1.5 g/dL during Weeks 1-24; $P < 0.01$; **Figure 8**)

Figure 8. IPSS-M risk downstaging and relationship of IPSS-M risk downstaging with Hb levels

[a]True signifies IPSS-M risk downstaging; false signifies no IPSS-M risk downstaging.
Hb, hemoglobin; IPSS-M, International Prognostic Scoring System-Molecular; NR, non-responder; R, responder; RBC-TI, red blood cell-transfusion independence.

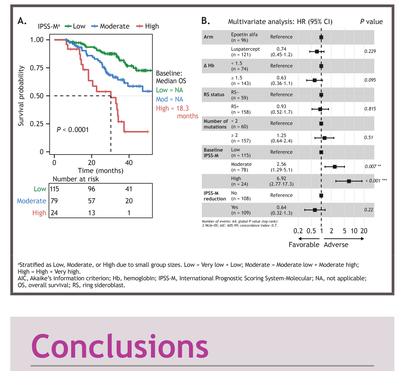
- Patients with IPSS-M risk downstaging experienced a longer Hb increase duration (≥ 1.5 g/dL) with luspatercept (21 months; $P = 0.045$) but not epoetin alfa (16 months; $P = 0.68$; **Figure 9**)

Figure 9. Association of IPSS-M risk downstaging and duration of Hb increase (> 1.5 g/dL)

[a]True signifies IPSS-M risk downstaging; false signifies no IPSS-M risk downstaging.
Hb, hemoglobin; IPSS-M, International Prognostic Scoring System-Molecular.

- Given the small sample size of the very low- and very high-risk subsets, IPSS-M risk categories were collapsed into 3 groups (low, moderate, high)
  - Baseline IPSS-M risk of the MDS cohort in the COMMANDS study was generally prognostic (**Figure 10A**), and the IPSS-M risk prognostic relationship appeared to hold at Week 24
- Using a multivariate Cox regression model (cutoff date, February 2025), luspatercept was associated with improved OS compared with epoetin alfa (HR, 0.58; 95% CI, 0.3-1.1) after adjusting for relevant variables, including change in Hb, RS status, mutational burden, baseline IPSS-M risk, and IPSS-M risk downstaging
- These COMMANDS analyses suggest that the OS benefit was influenced by multiple parameters (**Figure 10B**)
  - The most significant factor impacting OS was the baseline IPSS-M risk
  - Additionally, a trend was observed for improved OS with increased Hb levels (≥ 1.5 g/dL) and IPSS-M risk downstaging, both of which were more frequently seen with luspatercept treatment

Figure 10. Association of IPSS-M (and IPSS-M risk downstaging at Week 24) and its relationship to OS



[a]Stratified as Low, Moderate, or High due to small group sizes. Low = Very low + Low; Moderate = Moderate low + Moderate high; High = High + Very high.
AIC, Akaike's information criterion; Hb, hemoglobin; IPSS-M, International Prognostic Scoring System-Molecular; NA, not applicable; OS, overall survival; RS, ring sideroblast.

Conclusions

- This study examined the changes in somatic mutations and their relationship with clinical outcomes in patients with LR-MDS who were treated with luspatercept or ESA in the COMMANDS trial
- Importantly, reducing TB did not alter gene mutations or variants in either luspatercept or ESA by Week 48 and when stratified by RS status
  - These data align with the mechanism of action of luspatercept and the slower disease progression in patients with LR-MDS
- More frequent IPSS-M risk downstaging was seen in patients who were treated with luspatercept compared with ESA, in part due to improved Hb levels
  - Patients with IPSS-M risk downstaging experienced a longer duration of Hb increase with luspatercept treatment, but not in those treated with ESA
  - In this MDS biomarker cohort, baseline IPSS-M risk was prognostic of OS. In a multivariate analysis, a trend of improved OS was observed with luspatercept compared with ESAs. In addition, OS was influenced by multiple factors, including baseline IPSS-M risk, increased Hb levels, and IPSS-M risk downstaging
- OS in the luspatercept arm may be influenced by improvements in Hb levels and/or reduction in TB and appears independent of changes in gene mutations up to Week 48. Additionally, anti-inflammatory and cardioprotective mechanisms[10] could positively impact OS, and further analyses are needed to better understand these mechanisms

References

1. Platzbecker U et al. *Blood*. 2019;133:1020-1030.
2. Fenaux P et al. *Ann Oncol*. 2021;32:142-156.
3. Hennssen AJ, Walter MJ. *Blood*. 2020;136:50-60.
4. Papaemmanuil E et al. *Blood*. 2013;122:3616-3627.
5. Bersanelli M et al. *J Clin Oncol*. 2021;39:1223-1233.
6. Nazha A et al. *J Clin Oncol*. 2021;39:2234-2245.
7. Della Porta MG et al. *Lancet Oncol*. 2024;25:1461-1468.
8. Komrokji RS et al. *Hemasphere*. 2024;8(Supplement 1):1304.
9. Bernard E et al. *NEJM Evid*. 2022;1:EVIDoa2200008.
10. Hasan M et al. *Blood*. 2024;144(Supplement 1):4046.

Acknowledgments

- The patients and families who made this study possible
- The clinical study teams who participated
- The study was supported by Celgene, a Bristol Myers Squibb Company, in collaboration with Accelleron Pharma Inc., a wholly owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA
- All authors contributed to and approved the poster
- Writing and editorial assistance were provided by Alex Dimitri, PhD, of Lumanity Communications Inc., and were funded by Bristol Myers Squibb

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Presented at the European Hematology Association (EHA) Congress; June 12–15, 2025; Milan, Italy